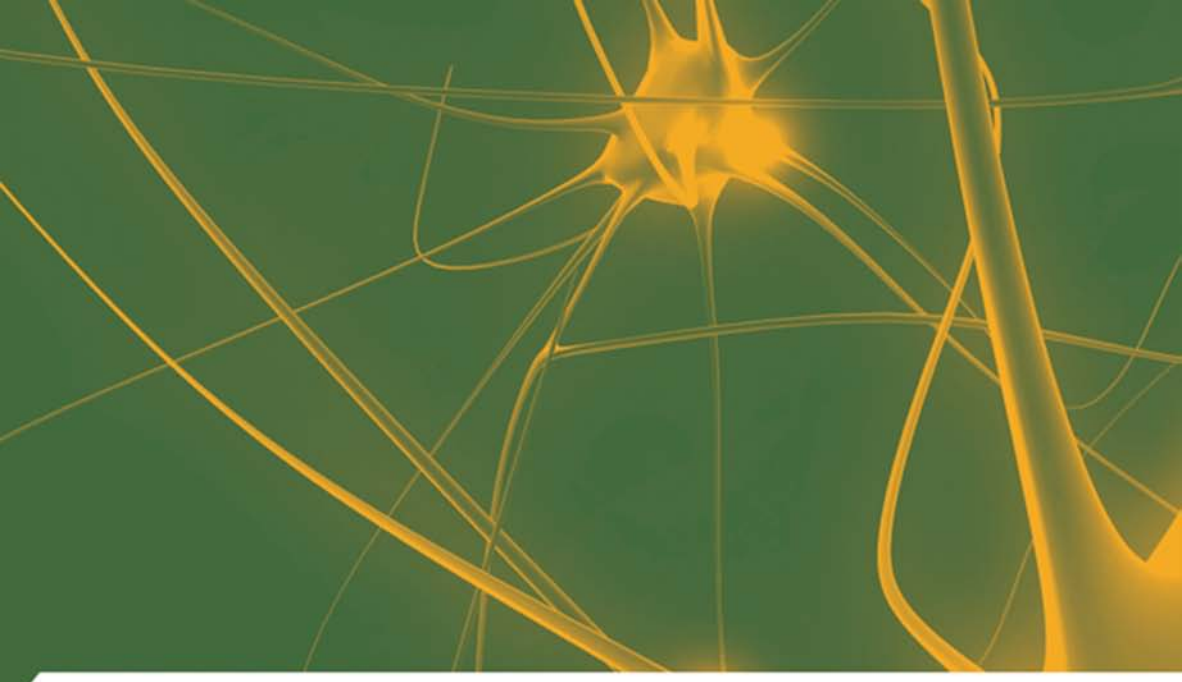

Neuropsychological Aspects of Substance Use Disorders

Evidence-Based Perspectives

Edited by

DANIEL N. ALLEN
STEVEN PAUL WOODS

Series on Evidence-Based Practices

OXFORD

Neuropsychological Aspects of Substance Use Disorders

National Academy of Neuropsychology Series on Evidence-Based Practices

SERIES EDITOR

L. Stephen Miller

SERIES CONSULTING EDITORS

Glenn J. Larrabee
Martin L. Rohling

Civil Capacities in Clinical Neuropsychology

Edited by George J. Demakis

Secondary Influences on Neuropsychological Test Performance

Edited by Peter A. Arnett

Neuropsychological Aspects of Substance Use Disorders

Edited by Daniel N. Allen and Steven Paul Woods

Neuropsychological Aspects of Substance Use Disorders

Evidence-Based Perspectives

Edited by Daniel N. Allen and Steven Paul Woods

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide.

Oxford New York
Auckland Cape Town Dar es Salaam Hong Kong Karachi
Kuala Lumpur Madrid Melbourne Mexico City Nairobi
New Delhi Shanghai Taipei Toronto

With offices in
Argentina Austria Brazil Chile Czech Republic France Greece
Guatemala Hungary Italy Japan Poland Portugal Singapore
South Korea Switzerland Thailand Turkey Ukraine Vietnam

Oxford is a registered trademark of Oxford University Press
in the UK and certain other countries.

Published in the United States of America by
Oxford University Press
198 Madison Avenue, New York, NY 10016

Library of Congress Cataloging-in-Publication Data
Neuropsychological aspects of substance use disorders : evidence-based perspectives / edited by
Daniel Allen and Steven Paul Woods.
pages cm—(National Academy of Neuropsychology series on evidence-based practices)
Includes bibliographical references and index.
ISBN 978–0–19–993083–8
1. Substance abuse—Treatment—Case studies. 2. Clinical neuropsychology. 3. Evidence-based
psychiatry. I. Allen, Daniel N. II. Woods, Steven Paul, 1972–
RC564.N476 2014
616.8—dc23
2013026889

9 8 7 6 5 4 3 2 1
Printed in the United States of America
on acid-free paper

To my wife Ann, for her steadfast support and friendship over these many years.

D.N.A.

To Kimberly, who for the past 20 years has kept me laughing and grounded, all the while being extraordinarilypatient and unwavering in her support (and tolerance) of my obsession with clinical neuropsychology. Also to my parents, who have been steadfast in their encouragement.And finally, to my mentors and students, who have inspired, challenged, and impressed me so very much along the way.

S.P.W.

Contents

Preface to the National Academy of Neuropsychology Book Series on Evidence-Based Practices

The field of clinical neuropsychology has advanced extensively and successfully in the worlds of psychology and neurology by following two major tenets. The first has been the constant focus on exploring and understanding the complex and intricate relationship between observed behavioral function and brain structure (and, of course, changes to that structure). From early observations of the relationship between brain injury and behavior to today's combination of psychometric testing, cognitive neuroscience, and functional neuroimaging techniques, this focus has served the field extremely well. The second has been the rigorous adherence to careful, replicable scientific principles of questioning and theorizing, data collection, and use of sophisticated statistical analysis in testing, evaluating, and interpreting information about brain/behavior relationships. It is in the spirit of this strong foundation of empirical evidence aimed at improving the quality of informed clinical decision-making that the National Academy of Neuropsychology (NAN) Series on Evidenced-Based Practices was developed and came to fruition.

For a significant amount of time, members of the neuropsychology community, and in particular the membership of the NAN, have voiced a desire for the development and availability of thorough and accurate resources that are directly applicable to the everyday needs and demands of clinical neuropsychology in a meaningful and accessible way, but provide the latest knowledge based on the most recent and rigorous scientific evidence within the field. The NAN Book Series on Evidence-Based Practices is meant to provide just such a series of resources.

At its inception, it was important to first identify an excellent publisher with a history of publishing significant psychological and scientific volumes who would share this vision and provide significant support for a quality product. After lengthy research and discussions with multiple publishers, the venerable Oxford University Press (OUP), one of the most renowned and respected publishing companies in existence, was selected by the NAN Board of Directors. For

their part, OUP have committed to the long-term development and support of the NAN Book Series and, as can be seen in the pages herein, they have spared no effort or expense to provide the finest-quality venue for the success of the Series.

The Book Series is designed to be a dynamic and ever-growing set of resources for the science-based clinical neuropsychologist. As such, the volumes are intended to individually focus on specific significant areas of neuropsychological inquiry in depth, and together cover the majority of the broad clinical area of neuropsychology. This is a challenging endeavor, and one that relies on the foremost experts in the neuropsychological field to provide their insight, knowledge, and interpretation of the empirically supported evidence within each focused topic. It is our hope that the reader recognizes the many established scholars from our field who have taken on the task of volume editor and chapter author.

While each volume is intended to provide an exhaustive review of its particular topic, there are several constants across the volumes. Importantly, each volume editor and respective chapter authors have committed to constraining themselves to providing only evidence-based information that meets that definition. Second, each volume maintains a broad consistency in format, including an introductory chapter outlining the volume, and often a final discussion chapter summarizing the state of the art within its topic area. Each volume provides a comprehensive index, and each chapter provides relevant references for the reader. Third, each volume is designed to provide information that is directly and readily usable, in both content and format, to the clinical neuropsychologist in everyday practice. As such, each volume and chapter within the volume is obliged to provide information in such a way as to make it accessible as a "pull off the shelf" resource. Finally, each volume is designed to work within a pedagogical strategy so that it educates and informs the knowledgeable neuropsychologist, giving a greater understanding of each particular volume focus, and provides meaningful (read "useful") information geared towards enhancing her/his practice of neuropsychology.

In keeping with the educational focus of the Series, an additional aspect is a collaboration of the Series contributors and the NAN Continuing Education Committee such that each Series volume is available to be used as a formal continuing education text via the CEU system of NAN.

It is my hope, and the hope of the consulting editors who provide their time, expertise, and guidance in the development of the NAN Series, that this will become an oft-used and ever expanding set of efficient and efficacious resources for the clinical neuropsychologist and others working with the plethora of persons with brain disorders and dysfunction.

L. Stephen Miller
Editor-in-Chief
National Academy of Neuropsychology
Series on Evidence-Based Practices
July, 2012

Preface to the Third Volume in the National Academy of Neuropsychology Series on Evidence-Based Practices

Substance use disorders continue to be a major health concern in the United States and worldwide. Clinical neuropsychologists are often asked to differentiate between the neuropsychological effects of a significant drug history versus the effects of current use, make judgments on whether a history of substance abuse is causally related to the onset of neuropsychological problems or potentially exacerbating comorbid neurological conditions, and comment on the risks of substance-related neuropsychological deficits for everyday functioning and outcomes (e.g., treatment adherence). Providing the latest empirical evidence regarding the specific sequelae and neuropsychological deficits associated with substance abuse disorders will assist clinicians in answering these questions, and that is the main objective of the current volume.

It is well known that substance use impacts brain structure and function, and may produce both acute and chronic neuropsychological abnormalities. While there is a large body of neuropsychological literature regarding some substances (such as alcohol) that dates back to the 1960s, the neuropsychological impact of other substances (e.g., methamphetamine) has developed much more recently. In concert with these recent developments in neuropsychology, a substantial body of knowledge regarding psychobiological, behavioral, and genetic factors that contribute to the onset and maintenance of substance use disorders has emerged. Similarly, translational research has attempted to move from these basic scientific findings to the development of evidence-based interventions for treatment of substance use disorders.

Substance use disorders make up one of the most prevalent major health challenges that we face today. They are pervasive, often chronic, afflict millions of persons worldwide, and have a major negative impact on society. The role of legal and illegal substances on neurocognition is complex and varied, and the subject of great controversy. Opinions about their relative influence on cognition differ across many dimensions, including acute or chronic impact, legal or illegal

substances, direct or indirect effects, or behavioral or genetic etiology, to name just a few issues.

Here, in this third volume of the National Academy of Neuropsychology's Series on Evidence-Based Practices—*Neuropsychological Aspects of Substance Use Disorders: Evidence-Based Perspectives*—Drs. Daniel N. Allen and Steven Paul Woods have brought together a remarkable group of international experts in substance use disorders and in neuropsychological measurement to provide a straightforward but detailed set of windows into these complex relationships. This important volume provides an empirically derived set of descriptions of the relationships between differing substances of abuse and neurocognition to inform researchers and practitioners alike, and make available the latest science examining these relationships.

Dr. Allen is the Lincy Professor of Psychology at the University of Nevada, Las Vegas. He is a Fellow of NAN and the American Psychological Association, and the current president-elect of NAN. He has received numerous awards for his scholarly work including the Nelson Butters Award and Early Career Award from NAN. He has had a longstanding interest in and a significant research history studying the comorbidity of substance use with other mental health disorders and their combined impact on neuropsychological performance. Dr. Woods is a Professor in the Department of Psychiatry at the University of California, San Diego, and received the 2007 Early Career Award for Contributions to Clinical Neuropsychology from NAN. His research interests focus on applying cognitive models of memory to examine central nervous system (CNS) effects of substance abuse and HIV infection. His work has been funded by the National Institutes of Health (NIH) and he has an extensive publishing record in some of our best neuropsychology journals. We are extremely fortunate to have two such productive, thoughtful, and accomplished volume editors. Importantly, both are also clinical neuropsychologists and have developed this volume to provide information of relevance to the practicing clinician.

This volume covers a wide variety of the most notable substances of abuse, from alcohol, cannabis, and cocaine, through "exotic" designer or club drugs, to prescription drug abuse. Each chapter goes into detail regarding the current empirical knowledge base of the role of each on neuropsychological performance, and, when appropriate, the impact of neurocognition on substance use. Additionally, there are substantive chapters on the neural substrates of addictions, the neuro-economic approaches to understanding the addiction process, the influence of genetics on addiction, and the multidirectional relationship of addictions treatment and neuropsychological impairment.

As are previous volumes in the Series, this volume is aimed primarily at neuropsychologists, but it should also be of use to a multitude of professionals who deal with the complexity of disentangling the interactions between cognitive processes, neuropsychological performance, and the many influences of substances of use and abuse.

L. Stephen Miller

Acknowledgments

First and foremost, we are indebted to the National Academy of Neuropsychology, without whom this volume in the Book Series on Evidenced-Based Practice would not have been possible. We are especially grateful for the guidance and wisdom of Series Editor, L. Stephen Miller, who has been a tremendous resource to us throughout this process. The initial review and comments of Consulting Editors, Glenn Larrabee and Martin Rohling were also instrumental in shaping the tone and content of this book. We also extend our gratitude to the authors of the various chapters in this edited volume, who took valuable time out of their very busy professional schedules to contribute to this effort. We are also appreciative of the invaluable assistance and support of Oxford University Press, with specialthanks to Joan Bossert, Vice President/Editorial Director in the Medical Division; Miles Osgood, Assistant Editor in the Academic Division; and our Project Manager, Joseph Lurdu Antoine, A. Finally, we also express our gratitude to the VA Healthcare System and National Institutes of Health (NIH), particularly the National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and National Institute of Mental Health (NIMH), who sponsored much of the science reviewed in this volume, and to the Lincy Foundation, for their support of education, medical, social service scientific research.

Contributors

Daniel N. Allen, Ph.D.
Lincy Professor of Psychology
Department of Psychology
University of Nevada Las Vegas
Las Vegas, Nevada

Marsha E. Bates, Ph.D.
Research Professor of Psychology
Director, Cognitive Neuroscience Laboratory
Center of Alcohol Studies
Rutgers, The State University of New Jersey
Piscataway, New Jersey

Sunita Bava, Ph.D.
Department of Psychiatry
University of California, San Diego
San Diego, CA

Lotte Berke, B.S.
Department of Psychiatry
University of California, San Diego
San Diego, CA

Veronica Bisagno
Instituto de Investigaciones Farmacológicas
(ININFA-UBA-CONICET)
Junín 956, piso 5, C1113-Buenos Aires, Argentina

Warren K. Bickel, Ph.D.
Director
Addiction Recovery Res earch Center
Virginia Tech Carilion Research Institute
Professor of Psychology
Virginia Tech
Virginia Tech Carilion Research Institute
Roanoke, Virginia

Kaitlin Blackstone
Graduate Student Researcher
SDSU/UCSD Joint Doctoral Program in Clinical Psychology
HIV Neurobehavioral Research Program
San Diego, California

Khalima Bolden, M.S.
Graduate Student Researcher
SDSU/UCSD Joint Doctoral Program in Clinical Psychology
Translational Methamphetamine AIDS Research Center
VA San Diego Healthcare System
San Diego, California

Lauren N. Buchheim, B.S.
Creighton University School of Medicine
Omaha, Nebraska

Jennifer F. Buckman, Ph.D.
Assistant Professor
Center of Alcohol Studies
Rutgers,The State University of New Jersey
607 Allison Road
Piscataway, New Jersey

Jean Lud Cadet, M.D.
Associate Director for Diversity and Outreach
Chief, Molecular Neuropsychiatry Research Branch
Co-Director, Fellowship in Addiction and Aging
National Institute on Drug Abuse (NIDA) Intramural Research Program
Baltimore, Maryland

Jason P. Caplan, M.D.
Associate Professor of Psychiatry
Chair of Psychiatry
Creighton University School of Medicine
St. Joseph's Hospital and Medical Center
Phoenix, Arizona

Norma Castro, M.A.
Department of Psychiatry
University of California, San Diego
San Diego, CA

Susan Cotton
Orygen Youth Health Research Centre
Centre for Youth Mental Health
University of Melbourne
Melbourne Australia

Jordan E. Cattie, M.S.
Graduate Student Researcher
San Diego State University/University of Calfornia, San Diego (SDSU/UCSD) Joint Doctoral Program in Clinical Psychology
HIV Neurobehavioral Research Program
San Diego, California

John C. Crabbe, Ph.D.
Professor, Behavioral Neuroscience
Senior Research Career Scientist, Research Service
Department of Veterans Affairs Medical Center
Director, Portland Alcohol Research Center

Rosemary Fama, Ph.D.
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, California

John E. Fisk, PhD
Professor of Psychology
School of Psychology
University of Central Lancashire
Preston, United Kingdom

Antonio Verdejo-García PhD
Departamento de Personalidad, Evaluación y Tratamiento Psicológico
Universidad de Granada
Granada, Spain

Igor Grant, M.D.
Distinguished Professor of Psychiatry
Director, HIV Neurobehavioral Research Program
University of California, San Diego
San Diego, California

Stefanie R. Griglak
Department of Psychiatry
University of California, San Diego (UCSD)
San Diego, California
Department of Psychology
Trinity College
Hartford, Connecticut

Marilyn Huckans, Ph.D.
Staff Psychologist and Neuropsychologist
Portland VA Medical Center
Associate Professor, Department of Psychiatry
Oregon Health and Science University
Portland VA Medical Center
Portland, Oregon

Jennifer E. Iudicello, Ph.D.
Postdoctoral Research Fellow
University of California, San Diego
HIV Neurobehavioral Research Program (HNRP)
Training in Research on Addictions in Interdisciplinary NeuroAIDS (TRAIN)
San Diego, California

David P. Jarmolowicz
Assistant Professor
Department of Applied Behavioral Science
University of Kansas
Lawrence, Kansas

Justine C. Bates-Krakoff
Department of Psychology
Pace University
861 Bedford Road
Pleasantville, New York

Bern G. Lee, B.A.
Ph.D. Candidate
Department of Psychology
University of Nevada, Las Vegas
Las Vegas, Nevada

Amanda M. Barkley-Levenson, B.S.
Ph.D. Candidate
Portland Alcohol Research Center
Department of Behavioral Neuroscience
Oregon Health & Science University and VA Medical Center
Portland, Oregon

Jennifer M. Loftis, Ph.D.
Associate Professor, Department of Psychiatry
Oregon Health and Science University
Research Scientist
Portland VA Medical Center
Portland, Oregon

Daniel I. Lubman
Turning Point Alcohol and Drug Centre
Eastern Health and Monash University
Melbourne, Australia

Kai-Hong Jeremy Mao, B.S.
Creighton University School of Medicine
Omaha, Nebraska

Thomas D. Marcotte, Ph.D.
Associate Professor of Psychiatry
University of California, San Diego
HIV Neurobehavioral Research Program
San Diego, California

Cherie L. Marvel
Dept. of Neurology, Division of Cognitive Neuroscience
Johns Hopkins University School of Medicine
Baltimore, Maryland

Miriam Z. Mintzer, Ph.D.
Associate Professor
Johns Hopkins University School of Medicine
Behavioral Pharmacology Research Unit
Behavioral Biology Research Center
Baltimore, Maryland

Catharine Montgomery, Ph.D.
Reader in Psychopharmacology
School of Natural Sciences and Psychology
Liverpool John Moores University
Tom Reilly Building, Byrom St,
Liverpool L3 3AF
United Kingdom

Olga Rass
Johns Hopkins University School of Medicine
Behavioral Pharmacology Research Unit
Behavioral Biology Research Center
Baltimore, Maryland

Derek D. Reed
Assistant Professor
Department of Applied Behavioral Science
University of Kansas
Lawrence, Kansas

Angelle Sander
Associate Professor
Department of Physical Medicine and Rehabilitation
Baylor College of Medicine
Houston, Texas

Rebecca L. Schacht
Johns Hopkins University School of Medicine
Behavioral Pharmacology Research Unit
Behavioral Biology Research Center
Baltimore, Maryland

J. Cobb Scott, Ph.D.
Assistant Professor
Yale University Department of Psychiatry
National Center for Post-Traumatic Stress Disorder
Clinical Neurosciences Division
VA Connecticut Healthcare System
New Haven, Connecticut

Tresa Roebuck Spencer, Ph.D.
University of Oklahoma
Cognitive Science Research Center
Norman, Oklahoma

Edith V. Sullivan, Ph.D.
Professor
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, California

Michael John Takagi, Ph.D.
Orygen Youth Health Research Centre
Centre for Youth Mental Health
University of Melbourne
Parkville, Australia

Susan F. Tapert, Ph.D.
Acting Chief, Psychology Service
VA San Diego Healthcare System
Professor of Psychiatry
University of California, San Diego
San Diego, California

Nicholar S. Thaler, Ph.D.
Post doctoral Fellow
Semel Institute
University of California, Los Angeles
Los Angeles, California

Erica Weber, M.S.
Graduate Student Researcher
SDSU/UCSD Joint Doctoral Program in Clinical Psychology
HIV Neurobehavioral Research Program
San Diego, California

Elisabeth A. Wilde, Ph.D.
Baylor College of Medicine,
Departments of Physical Medicine and Rehabilitation, Neurology, and Radiology and
Michael E. DeBakey Veterans Affairs Medical Center, Traumatic Brain Injury Center of Excellence
Houston, Texas

Steven Paul Woods, Psy.D.
Professor of Psychiatry
University of California, San Diego
HIV Neurobehavioral Research Program
Translational Methamphetamine AIDS Research Center (TMARC)
Training in Research on Addictions in Interdisciplinary NeuroAIDS (TRAIN)
San Diego, California

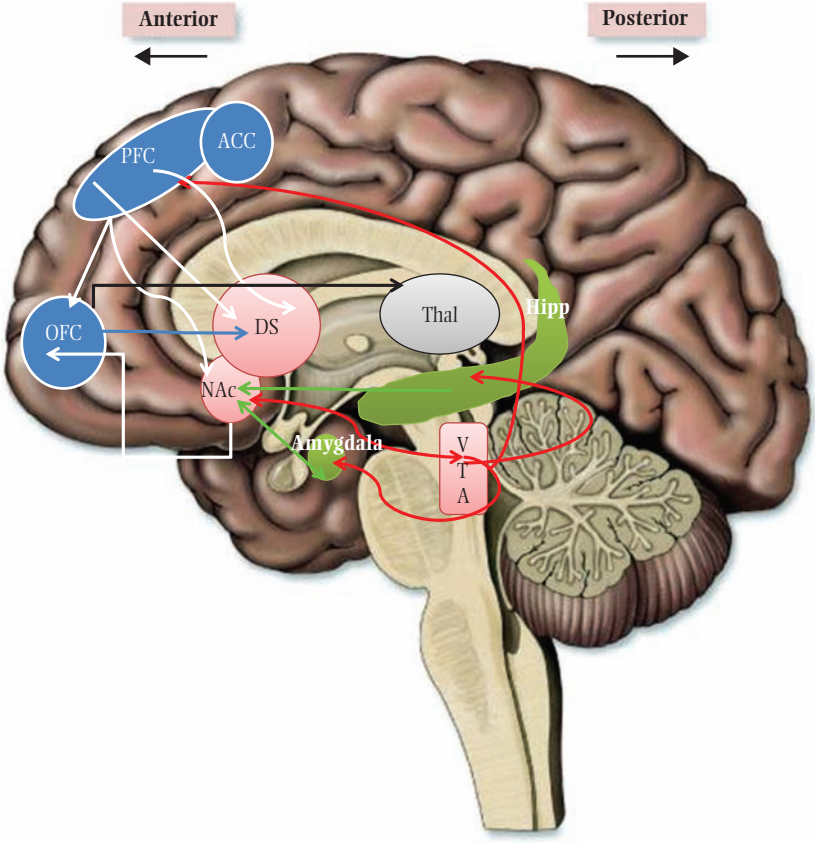

Figure 2.1 Mesocorticolimbic reward circuit. Regions of the brain that are involved in reward and addiction: the ventral tegmental area (VTA) ventral striatum (nucleus accumbens, NAc) involved in responding to rewarding stimulus; the amygdala and hippocampus (Hipp), which participate in memory functions; the mediodorsal thalamus, key component of thalamo-cortico-basal ganglia circuits implicated in aberrant habit-learning disorders; and the prefrontal cortex/orbitofrontal cortex (PFC/OFC) and anterior cingulate cortex (ACC), which participate in executive control and emotion regulation.

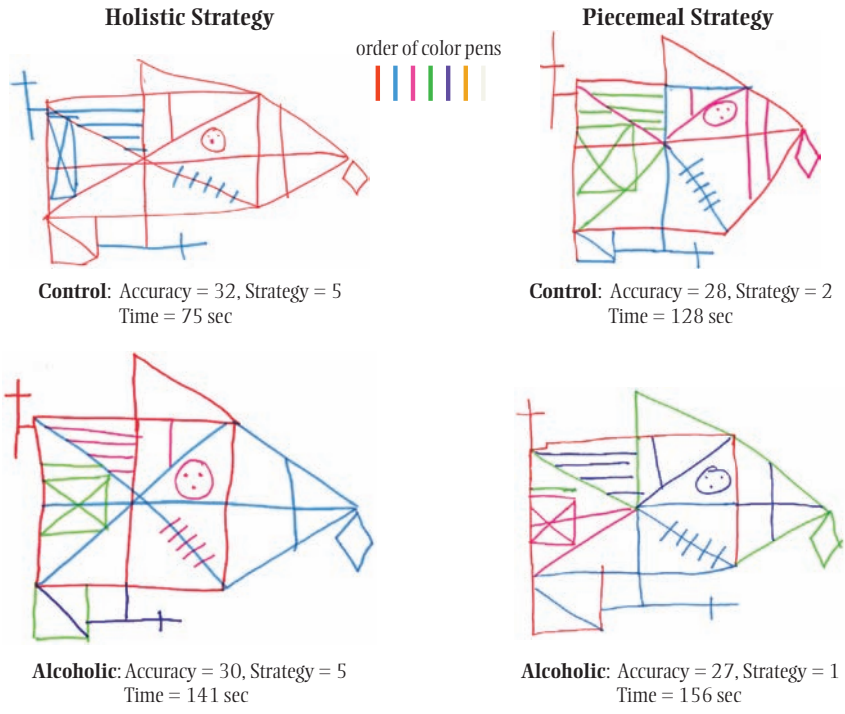

Figure 6.1 Examples of drawings copied by controls (*above*) and alcoholics (*below*) illustrating holistic (*left*) and piecemeal (*right*) strategies. Subjects drew first with a red pen, then with a blue pen, a pink pen, and a green pen, using each for 30 seconds.
Modified from Rosenbloom et al., *Brain Imaging and Behavior* (2009).

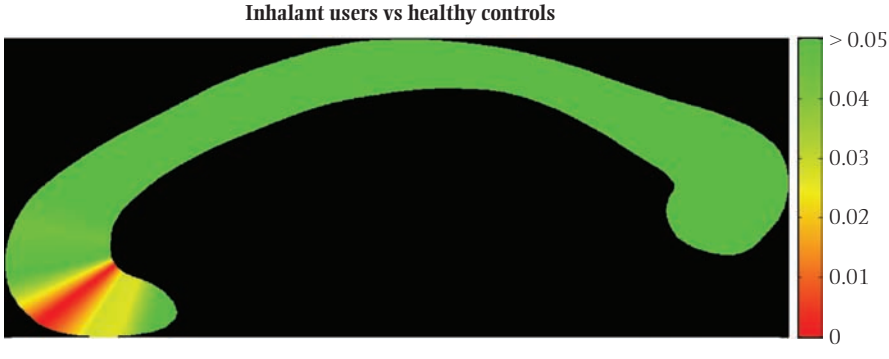

Figure 12.3 Regional callosal-width alterations for inhalant versus community controls, with significant and trend-level expansions denoted by color-coding according to significance.*
*Reproduced from Takagi et al. (2011).

1

Introduction

DANIEL N. ALLEN AND STEVEN PAUL WOODS

> *I have absolutely no pleasure in the stimulants in which I sometimes so madly indulge. It has not been in the pursuit of pleasure that I have periled life and reputation and reason. It has been the desperate attempt to escape from torturing memories, from a sense of insupportable loneliness and a dread of some strange impending doom.*
>
> — Edgar Allan Poe[1]

Substance use disorders continue to be a major health concern in the United States and worldwide, although their causes and effective treatments remain elusive. What is clear is that they are responsible for a great deal of public health burden, bringing great distress and harm to those who have the disorders, as well as their family members, friends, and the healthcare system. This burden is compounded the by presence of comorbid psychological, emotional, social, and medical dysfunctions, which for some drive the development of substance abuse and for others are a consequence of it. There is now a substantial body of evidence that substance use directly impacts brain structure and function, providing insights into a number of mechanisms that put some individuals at increased risk to transition from recreational use to addiction. It is also well documented that some substances have higher addictive potential and produce greater negative physical, psychological, and neurological effects compared to others, with evidence from postmortem and antemortem human investigations, animal studies, and in

1. From S. H. Whitman (1860). *Edgar Poe and His Critics*, pp 74–75. New York: Rudd & Carleton.

vitro modeling demonstrating greater neurotoxic effects of some substances over others. Persisting neural injury and associated neuropsychological abnormalities associated with prolonged and heavy use are oftentimes the motivation for referral to clinical neuropsychologists for evaluation. In this context, clinical neuropsychologists are often asked to differentiate between the neuropsychological effects of a significant drug history versus the effects of current use, make judgments about whether a history of substance abuse is causally related to the onset of neuropsychological problems or potentially exacerbates neuropsychological deficits resulting from preexisting and commonly comorbid neurological or psychiatric disorders, and comment on the adverse impact of substance-related neuropsychological deficits on everyday functioning; for example, treatment adherence, ability to manage finances, and job fitness. In forensic settings, neuropsychological evaluation may be requested to provide insight into substance-induced neuropsychological deficits as a mitigating factor in sentencing.

While neuropsychological studies of substances such as alcohol began to appear in the neuropsychological literature as early as the 1960s and 1970s (Goldstein & Chotlos, 1965, 1966; Jones & Parsons, 1971; Tarter & Parsons, 1971), it is only more recently that scientists have begun to intensely investigate the consequences of other commonly abused drugs on neurological integrity and associated neuropsychological functioning. In fact, over the past two decades, the literature documenting the neurophysiological effects of various substances has virtually exploded. This literature has documented neuropsychological abnormalities and provided insights into psychobiological, behavioral, and genetic factors that contribute to the onset and maintenance of substance use disorders and associated neuropsychological abnormalities. Translational research has attempted to move these basic scientific findings from the bench to the bedside, supporting development of evidence-based prevention and intervention programs that target substance use and abuse, considering, among other things, the manner in which neuropsychological deficits interact with treatment effectiveness and outcome. This research has provided a strong empirical foundation that has direct implications for clinical neuropsychological practice. However, given the diverse nature and sheer volume of this work, there is an evident need to provide the practitioner with a cogent and up-to-date summary of current developments, which is the goal of this volume. Chapters in this volume provide the latest empirical evidence regarding epidemiological, genetic, and psychobiological factors that contribute to the development and maintenance of substance use disorders, as well as their associated social, behavioral, psychiatric, and neuropsychological sequelae, in order to assist clinicians in answering relevant referral questions.

In the following introductory sections, we provide a brief history of substance use and abuse, including consideration of legislative efforts to control access, distribution, and use; incidence and prevalence of substance use disorders in the United States; a review of current diagnostic practices with regard to substance-related disorders, including general issues regarding assessment of substance use disorders in the clinic; tailoring assessment batteries to increased sensitivity to the effects of such substances; as well as an overview of the organization of the book and contents of its chapters.

A BRIEF HISTORY OF SUBSTANCE USE AND ABUSE

Ancient History

Archeologists have provided abundant evidence for the use of psychoactive substances dating back to prehistoric times. Production and use of alcohol may date as far back as 9000 years in China's Henan province, with archeological evidence documenting wine making and viniculture to the Neolithic period, as early as 5400–5000 B.C. (McGovern et al., 2004). Infrared and chemical analyses of ancient clay jars dating back to 5400–5000 B.C. found in a mud-brick building in the Hajji Firuz Tepe in the Zagros mountain of present-day Iran (see Figure 1.1) clearly indicated the presence of chemicals that were common to wine production (McGovern et al., 1997). These included high amounts of tartaric acid, which only naturally occurs in large amounts in grapes, as well as natural preservatives derived from tree resins, which are later well documented in wine production in ancient Egypt and the Near East. Stoppers were also found at the Hajji Firuz Tepe site, which would have allowed sealing of the jars to prevent the grape product from turning from wine to vinegar. At the beginning of the Old Kingdom Period of Egypt

Figure 1.1 Neolithic jar used to store wine, found at Hajji Firuz Tepe (Iran).*
From: McGovern, P. E., Hartung, H., Badler, V. R., Glusker, D. L., & Exner, L. J. (1997). The beginnings of winemaking and viniculture in the ancient Near East and Egypt. *Expedition, 39*(1), 3–21. Used with permission. All rights reserved. * One of six jars once filled with resinated wine from the "kitchen" of a Neolithic residence at Hajji Firuz Tepe (Iran), dating back to 5400–5000 BC. *UPM no. 69012015. H. 23.5 cm. Photograph courtesy of Hasanlu Project, University of Pennsylvania Museum*.

(ca. 2700 B.C.), there was also clear evidence for large-scale wine production. Scenes depicting wine-making were illustrated on tomb walls, with wine included as a common provision for the afterlife, sealed in wine jars (see Figure 1.2).

Archeological evidence also supports the early use of other substances, such as opium and cannabis. Earliest documentation of opium use dates back to the third millennium B.C. Clay tablets found in the ruins of the city of Nippur just south of Baghdad dating back to 3400 B.C. indicate that Sumerians in Mesopotamia cultivated opium poppies in order to isolate opium (Brownstein, 1993; Schiff, 2002). Opium was also used in ancient Egypt, although restricted to occasions such as religious ceremonies and rituals. There is also evidence for opium use from Greek and Roman literature, in Arabia, and later its introduction into China between the eleventh and thirteenth centuries A.D. by Arabian traders (Schiff, 2002). The use of cannabis for medicinal purposes may date back to circa 2700 B.C., where Chinese

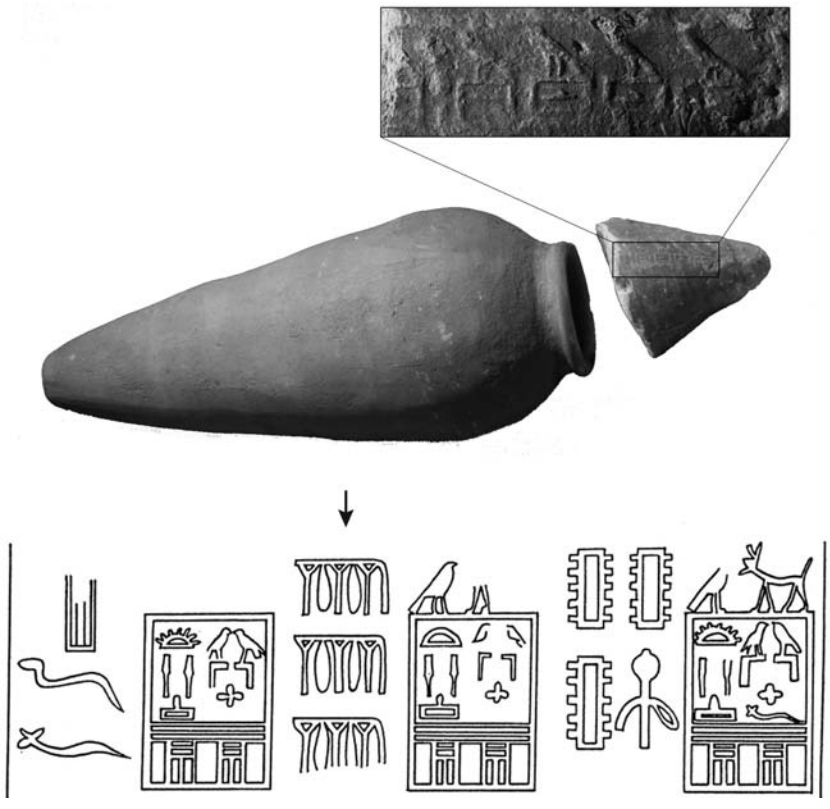

Figure 1.2 Early Dynastic wine jar from royal tomb in Egypt.*

From: McGovern, P. E., Hartung, H., Badler, V. R., Glusker, D. L., & Exner, L. J. (1997). The beginnings of winemaking and viniculture in the ancient Near East and Egypt. *Expedition, 39*(1), 3–21. Used with permission. All rights reserved. * (a) Early Dynastic "wine jar" from a royal tomb at Abydos, Egypt, with stopper showing serekh (the early hieroglyphic form of the cartouche) of Den, a Dynasty 1 pharaoh (see insert). (b) The early hieroglyphic sign for "grapevine/vineyard" (arrowed) occurs on a more elaborate cylinder seal impression on a jar stopper with the serekh of Khasekhemwy, a Dynasty 2 pharaoh. (a) UPM no. E6943. H. 66.5 cm (Petrie 1901:I:29, pls. 40.26 and 52.743); unprovenanced stopper UPM no. 60-15-23. Photograph courtesy of the Egyptian Section, UPM, modified by P. Zimmerman, MASCA. (b) Drawing after Kaplony 1963-64; Fig. 310.

Figure 1.3 Chinese ideogram for marijuana.
The Chinese ideogram for marijuana ("ma") shows two plants, male and female, under a drying shed.
From Aldrich, M. (1997). History of Therapeutic Cannabis. In M. L. Mathre (Ed.), *Cannabis in Medical Practice,* p. 36. Jefferson, NC: McFarland and Company Inc.

legend attributes to Emperor Chen Nung the discovery of its healing properties (Mack & Joy, 2000). Early Chinese medical writings include a pictogram for marijuana (see Figure 1.3) depicting two plants drying under the roof of a shed (Marthe, 1997). There is also evidence for the use of cannabis in religious rituals in India as early as 2000 B.C., with medicinal use described in Greek and Roman writing as early as A.D. 1–25 (Mack & Joy, 2000).

Modern History

Following the Middle Ages, substance use patterns in Europe were largely influenced by expanding exploration of the New World. Brecher (1972) provides a detailed history of substance use and abuse, and notes that in a relatively short period of time, substance use patterns in Western Europe shifted from a primarily alcohol-based culture to become a multi-drug culture. Tobacco was introduced to Europe by sailors who had explored the New World and learned to use tobacco (both smoking and chewing tobacco leaves) from American Indians. Caffeine was introduced to Europe by explorers and traders who discovered coffee in Turkey and Arabia, the kola nut in Western Africa, and tea produced largely in China. Peyote had been used by the Aztecs as part of religious rituals dating back to pre-Columbian times, and Incan rituals involving peyote and the chewing of leaves from the coca plant were encountered by the Spanish conquerors of Mexico. While cocaine was not isolated from coca leaves until 1844, the use of coca leaves occurred long before then. Although cannabis use dates back to 2000 B.C. in Chinese culture, the plant was not indigenous in the New World. It was introduced to Chile by the Spaniards in 1545, and was later cultivated by Jamestown settlers and elsewhere as early as 1611, where it was grown for hemp

fibers (Brecher, 1972). While isolation of opium from poppies dates back to as early as 3400 B.C. (Brownstein, 1993), it was not until the early nineteenth century that opium became a part of European and American cultures. In the United States, opium was used for medicinal purposes from the early to mid 1800s, primarily as an analgesic, but also for treatment of a variety of "nervous" conditions. Schiff (2002) indicates that, during the Civil War, the "Union Army used 2.8 million ounces of opium tincture and powder and about 500,000 opium pills" (p. 189). Recreational use of opium was fueled by a number of influences, including its spread across the country by Chinese workers who were building the transcontinental railroad in the 1860s (Brecher, 1972). Although its use was primarily medicinal at that time, recreational use of opium (typically smoking) did occur, and its potential for addiction and associated negative consequences were also clearly documented (Levine, 1974).

Reasons for Substance Use

The reasons for substance use in ancient times closely mirror those of today. For alcohol, not only was it used for medicinal purposes over the millennia, but it had a number of other beneficial aspects that increased life expectancy and reproductive success, such as counteracting potentially harmful microorganisms in water supplies, increasing the nutritive value of the natural product, and decreasing the risk of developing a number of medical conditions (McGovern, 2009). Use of naturally occurring substances for medicinal purposes is also well documented. For example, early Hindu texts describe some of the benefits of alcohol use, concluding that alcohol has medicinal purposes if used in moderation (Dasgupta, 2011). Use of substances was also an integral part of religious ceremonies and rituals through the ages, with some of the more common examples including the use of peyote in the Native American Church and the service of wine during Communion and the Eucharist in the Christian religion. Finally, it is clear that alcohol and other drugs have been used for their hedonic effects since ancient times.

Thus, while many of these substances were initially used for medicinal or religious purposes, recreational use was also common, prompting legislative efforts and cultural and religious prohibitions to control the misuse of substances since our earliest recorded history. Writings from religious and other sources highlight the potential negative consequences of substance misuse, acknowledging the negative effects that substance intoxication has on human reasoning processes as well as the potential of repeated intoxication for development of what are now referred to under current diagnostic practice as "substance abuse" and "substance dependence." The *Panchsheel* in Buddhism, dating back to 5000 B.C., warns against intoxication out of respect for a clear mind (Dasgupta, 2011). Sumerian wisdom literature from the *Shuruppak* texts dating back to three millennia B.C. suggest, "A drunkard will drown the harvest" (Lambert, 1996). Similarly, there are Jewish and Christian prohibitions against alcohol intoxication. In the Old Testament, Proverbs 23:29–30 says, "Who has woe? Who has sorrow? Who has strife? Who

has complaints? Who has needless bruises? Who has bloodshot eyes? Those who linger over wine.…" And in the New Testament: "Do not get drunk on wine, which leads to debauchery.…" (Ephesians 5:6). Consumption of alcohol and other intoxicants is prohibited in Muslim cultures because of their adverse effects on the body and mind. While many of these ancient writings also acknowledge the potentially beneficial aspects of some substances, their prohibitions against substance intoxication resonate with modern understandings of the deleterious effects that substances may have on our physical health, cognition, and psychosocial functioning.

With regard to formal legislation, in the United States, the first law regulating opium was passed in California in 1872, with the Territory of Oregon passing the first comprehensive substance abuse law in 1877, making it illegal for anyone to possess opium, cocaine, and a number of other substances, without a prescription (Levine, 1974). Some years later, similar legislation was introduced in various states to prohibit peyote use. Prohibitions against tobacco use began in the early part of the twentieth century, with laws prohibiting cigarette smoking in fourteen states by 1921 (Brecher, 1972). During the same period, alcohol prohibition movements were common and eventually resulted in the Eighteenth Amendment to the United States Constitution, making it illegal to produce, transport, or sell alcohol (Brecker, 1972). This led to an era commonly referred to as "Prohibition" in the United States, which began in 1920. The Eighteenth Amendment was eventually repealed in 1933 due to public opposition, among other considerations, as were many anti-tobacco laws, highlighting the very real tensions that continue to exist between drug policy, public opinion, and drug use. Legislation prohibiting the use of marijuana also began as early as 1927, when Louisiana passed legislation including fines and imprisonment for the possession or sale of marijuana (Brecker, 1972). Efforts to control substance use at the state levels were characterized by a lack of uniformity and were challenged to keep pace with the emergence of new substances, such as barbiturates, amphetamines, and LSD (lysergic acid diethylamide). These considerations prompted federal legislation, beginning in 1906 with the passage of the Pure Food and Drug Act, which, among other things, required that medicines containing opiates be labeled as such, with a clear indication of the amount of opiates contained (Brecker, 1972). Formation of the Federal Bureau of Narcotics (later renamed the "Drug Enforcement Administration") occurred in 1932, followed shortly thereafter by the proposal of the "Uniform Anti-Narcotics Act" and passage of the "Marihuana Tax Act" in 1937 (Brecker, 1972). Efforts at the federal level culminated in the passage of the "Controlled Substances Act" in 1970, which was the first comprehensive legislation providing integrated regulations to implement legal control over the burgeoning number of natural, semi-synthetic, and synthetic compounds that had become substances of abuse at that time. Included in this legislation were five separate "schedules" that attempted to classify substances based on their accepted medical uses and their potential for abuse, and stipulated penalties for violations in each schedule based on whether the individual was considered a "user," an "addict," or a "trafficker" of the substance. The most severe penalties were specified for drugs classified in

Schedule I, which includes marijuana, heroin, and LSD, among others, while the least severe penalties were specified for Schedule V drugs, which included substances that could be sold over the counter without a prescription, such as cough syrups. The legislation also allowed for the classification of new drugs under each of the five schedules, and was notable in its call for increased research in the areas of prevention and treatment. Thus, history provides a clear picture of the tensions that exist today between the use of substances for recreational, religious, and medicinal purposes, with the ever present potential for addiction and the negative consequences that result therefrom.

EPIDEMIOLOGY

Each of the chapters in Section II of this volume provides relevant epidemiological information for specific substances, so here we will discuss more general current trends in substance use disorders. Estimates indicate that 18.9 million adults in the United States were diagnosed with substance abuse or dependence in 2011, or approximately 8% of the adult population (Substance Abuse and Mental Health Services Administration [SAMHSA], 2012). Approximately 23.5 million Americans age twelve and older required intervention for substance use (SAMHSA, 2010). Treatment and other related costs in the United States resulting from substance-related disorders has been estimated to be $510.8 billion (Miller & Hendrie, 2009). It is projected that disability caused by substance use disorders will surpass that caused by any other physical disease worldwide by 2020 (World Health Organization, 2004). It is apparent from these and other statistics that substance use disorders are a major public health concern in the United States and worldwide.

There are numerous socioeconomic and sociopolitical factors that assist in understanding changes in drug use over time. One is the relative accessibility of illicit substances within the general population. Increased access is associated with increased use, so much effort has been directed toward limiting the availability and access to both licit and illicit substances, through drug enforcement policy targeting the import and distribution of illicit drugs, age restrictions, increased taxes, and restriction of use in public places for licit substances like tobacco and alcohol. These efforts have met with mixed success, as evidenced by epidemiological studies indicating that substance use in the general population for specific substances exhibits divergent trends, with the use of some substances increasing and the use of others decreasing over the same time periods. Public policy, sociopolitical influences, and psychological factors such as the perceived risk of negative consequences associated with use of a particular substance play an important role in incidence of use, so efforts to prevent or decrease substance use have often focused on educating the public regarding the risks of use. These efforts have often focused on adolescents, since risk-perception is an important factor influencing decisions to use substances, such that adolescents who perceive a high risk of harm from substance use are less likely to use than those who perceive a low risk of harm (Johnston, O'Malley, Bachman, & Schulenberg, 2012).

Some cases in point include recent trends regarding adolescent and young adult use of alcohol, tobacco, and marijuana (SAMHSA, 2010, 2012, 2013). Changes in alcohol use and risk perception from 2002 to 2011 among adolescents ages twelve to seventeen indicate that past-month binge alcohol use decreased to an all-time low of 7.4% for past-month episodes in 2011, from 10.7% in 2002. This decrease in use was accompanied by a commensurate increase in the perception of great risk from binging of 38.2% in 2002 to 40.7% in 2011. Incidence of drinking by underage individuals twelve to twenty years of age also declined, from 28.8% in 2002 to 25.1% in 2011, as did the number of individuals twelve and older who had driven under the influence of alcohol during the past year, from 14.2% in 2002 to 11.1% in 2011.

The dissociation between public policy, sociopolitical influence, incidence of drug use, and perceived risk is also apparent when comparing the data for alcohol and tobacco use with changes in marijuana use rates over the past twenty years. As mentioned before, cannabis is classified as a Schedule I substance according to the 1970 Controlled Substance Act, making it comparable to drugs like heroin with regard to legal penalties for use, possession, and distribution. However, there has been a move toward legalizing marijuana in a number of states, accompanied by an increased public perception of the acceptability of its use. Polling data in 1969 indicated that 84% of Americans were against legalizing marijuana, while 12% were in favor of it, compared with 2011 data indicating 46% of American are against legalization and 50% are in favor of it (Gallup Politics, 2013). At the same time, the perception of negative consequences associated with cannabis use have decreased among adolescent users, from their peak in 2005, when 55.0% of adolescents perceived risk of great harm from smoking marijuana once a month, to 44.8% in 2011. Over this same period, the percentage of adolescents reporting marijuana use over the past month has increased from 6.8% in 2005 to 7.9% in 2011 (SAMSHA, 2013).

Whether efforts designed to increase awareness of risks associated with tobacco and alcohol use through media campaigns, educational programming, and other efforts are causally related to decreases in alcohol use and smoking among adolescents, and increases in marijuana use, cannot be determined. However, the findings regarding alcohol and tobacco use do support an apparent relationship between increased perceived risk and decreased reporting of substance use, and are also consistent with opposite trends noted for drugs such as marijuana. Thus, while the causal relationships between changes in public policy, social acceptability, perceived risk, and incidence of use cannot be directly determined, the interrelationship between them nevertheless does highlight the fact that the incidence of use of any substance is most likely determined by factors other than, or in addition to, the psychoactive effects and additive properties of a particular substance.

CURRENT DIAGNOSTIC PRACTICES

The two most common diagnostic systems for substance related disorders include the *International Classification of Diseases–10* (ICD-10) and the *Diagnostic and*

Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). There are differences between these two classification systems: for example, the ICD-10 includes diagnostic categories for Harmful Use and Dependence Syndrome, while the DSM-IV-TR labels generally comparable disorders as Substance Abuse and Substance Dependence. However, they also have much in common, and efforts have been made to develop comparable diagnostic criteria across both systems, so we will focus our discussion on the DSM-IV-TR diagnostic criteria, which are in common use in the United States. The DSM-IV-TR classifies disorders arising from the use of substances under the general category of Substance-Related Disorders. Within this general category, there are two main subcategories that include Substance Use disorders and Substance-Induced disorders. Substance use disorders include the diagnoses of Substance Abuse and Substance Dependence. These two diagnoses constitute the most common Substance-Related disorder diagnoses. Substance-Induced disorders include conditions whose causes are thought to be etiologically related to the use of substances, such as withdrawal effects from cessation of cocaine use, psychotic symptoms caused by the use of amphetamines, or dementia caused by the neurotoxic effects of alcohol.

Substance Use Disorders (Abuse and Dependence)

Substance Abuse is diagnosed when it is determined that substance use has led to significant recurrent negative consequences in one or more of four domains over the same 12-month period. These domains include legal, interpersonal, work, or school, or hazardous behaviors. Examples of behaviors that would meet these criteria include a failure to fulfill major role obligations at work, at school, or in the family; use of substances in situations where their intoxicating effects increase the risk of physical harm (such as driving a motor vehicle); or repeated interpersonal problems that are associated with substance use. Some have suggested that individuals falling in this diagnostic category may be more accurately characterized by the term "substance misuse," since physiological dependence and a pattern of compulsive use are not required to make this diagnosis.

A Substance Dependence diagnosis is made when substance use persists despite leading to three or more recurrent negative cognitive, behavioral, or physiological consequences over a 12-month period. Symptoms meeting criteria may include physiological dependence as indicated by tolerance or withdrawal, unsuccessful attempts to cut down use even though desiring to do so, using substances in larger doses or for longer periods of time than originally intended, spending substantial time in the procurement or use of substances or recovering from their effects, failure to fill major role obligations as a result of substance use, or continuing to use substances despite the knowledge that they worsen current medical or psychiatric conditions. Thus, a major distinction between substance dependence and substance abuse is the compulsive use of the substances with an inability to control their use, despite the realization that use causes negative consequences.

The diagnostic criteria for substance dependence also include an indicator for the presence of physiological dependence, since physiological dependence is not required to make the diagnosis, but it is an important treatment consideration when withdrawal effects are expected as a result of substance use cessation. Finally, the DSM IV-TR provides six course specifiers for a diagnosis of substance dependence, four that allow the clinician to indicate different states of remission (partial early or partial sustained remission, and full early or full sustained remission), as well as two indicators to identify whether the individual is on an agonist therapy or in a controlled environment.

Substance Abuse and Dependence diagnostic criteria are applied to 13 categories of substances in the DSM: Alcohol, Amphetamines, Caffeine, Cannabis, Cocaine, Hallucinogens, Inhalants, Nicotine, Opioids, Phencyclidine; and Sedatives, Hypnotics, and Anxiolytics, as well as two other categories, Polysubstance and Other. The Other category is used for substances that are not included in the 13 specific drug categories (e.g., anabolic steroids, some over-the-counter and prescription medications). In addition, if a diagnosis of substance dependence is present for a specific substance, a Substance Abuse diagnosis cannot also be given for that same substance. However, in the case of polysubstance use, which is quite common, multiple diagnoses can be made. For example, an individual could be diagnosed with alcohol dependence, cocaine abuse, and cannabis abuse. There is a special diagnostic category of Polysubstance Dependence, which is only diagnosed when an individual who uses multiple substances does not meet criteria for dependence on any of those substances when considered individually, but when the combined effects of the individual substances are considered together, the individual would meet diagnostic criteria for substance dependence.

Substance-Induced Disorders

While substance-induced disorders are less common than substance use disorders in most outpatient settings, they are important to consider when evaluating individuals who use substances. These disorders include substance intoxication, substance withdrawal, as well as eight other substance-induced psychiatric disorders (substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction, and sleep disorders). The diagnoses of substance intoxication and substance withdrawal are relatively straightforward when the substance responsible for these conditions has been identified. Sometimes, in cases where multiple substances are being used at the same time, associations between withdrawal or intoxication effects with a particular substance can be more difficult to establish.

For the other substance-induced disorders, it can be quite challenging to make the diagnosis, because it is often unclear whether the psychiatric symptoms are better characterized as stemming from a primarily psychiatric or primarily neurological disorder, or rather result from the use of a particular substance. The criteria itself require that there be evidence from physical examination, laboratory studies, or subject history that establishes an etiological link from the substance

use to the substance-induced disorder. Even when such information is available, the temporal associations between the substance-induced diagnosis under consideration and patterns of substance use can be difficult to establish. For example, in the case of an individual with heavy alcohol use and periodic depressive episodes, it is not always clear whether the alcohol use preceded the onset of depressive symptoms or, alternatively, whether alcohol was used in attempt to cope with preexisting symptoms of depression. Collateral sources of information such as family members or other informants and available medical records can be helpful in establishing the temporal associations between onset of substance use and the emergence of psychiatric symptomatology. However, even in cases where an adequate patient history is available, there is often a good deal of clinical judgment used in establishing these diagnoses. Clinical decision-making may be further informed by considering a number of factors such as family history of mental disorder, prior episodes of the disorder under consideration, and whether or not psychiatric symptoms are consistent with typical intoxication or withdrawal effects for various substances. For example, onset of major depressive symptoms during alcohol intoxication is consistent with the physiological effects of the substance; however, similar symptoms during methamphetamine intoxication are not consistent with the physiological effects of the drug. In the former case, a diagnosis of alcohol-induced mood disorder could be considered, but in the latter case it could not. When the disorder does not occur during intoxication or withdrawal, it must begin within one month of cessation of drug use. Psychiatric symptoms that persist for longer than a month may be better classified as a primary psychiatric disorder. For example, in the case of an individual who begins experiencing psychotic symptoms during methamphetamine intoxication or withdrawal, if the psychotic symptoms continue to persist over months, the diagnosis might be changed to a primary psychotic disorder, with substance use considered an environmental risk factor that contributed to the onset of a psychotic disorder in an individual who was already predisposed to develop one.

It is also noteworthy that neuropsychologists are uniquely trained to evaluate at least two of these disorders: Substance-Induced Persisting Dementia, and Substance-Induced Persisting Amnestic Syndrome. As with the other disorders, the link between substance use and the onset of these neurological conditions requires extensive history-taking, and it can be difficult to establish the etiological link from the substance to the disorder itself. However, neuropsychological evaluation may provide very useful information that helps establish differential diagnoses between dementia and amnestic disorders, as well as provide evidence that will assist in differentiating substance-induced persisting dementia from other forms of dementia. Specifically, since well-established profiles of neuropsychological functioning are available for many degenerative dementias, comparisons between the cognitive profiles of individuals suspected to have substance-induced persisting dementia with those having other established conditions may provide invaluable information in arriving at the correct diagnosis. A final point of clarification is that, like the substance use disorders, substance-induced disorders are diagnosed according to the 13 drug categories previously described. However, not all substance-induced disorders can be caused by all 13 drug categories. For example, while there are diagnoses

for cocaine-induced psychotic, anxiety, and sleep disorders, there are no diagnoses for Cocaine-Induced Persisting Dementia or Persisting Amnestic Disorder.

DSM-V

The DSM-V is slated for publication in the summer of 2013 and is purported to incorporate a number of significant changes to the Substance-Related Disorders diagnostic criteria. At the time of this publication, the general title of the category is slated to be changed from Substance-Related Disorders to Substance-Related and Addictive Disorders. This change was incorporated in order to allow other non-substance-related addictive disorders to be included as the subcategory Non-Substance-Related Disorders, which includes the DSM-IV diagnosis of Pathological Gambling that was formerly classified as an Impulse Control Disorder and is now referred to as Gambling Disorder. Another major change was the combining of the DSM-IV Substance Abuse and Dependence diagnoses into the single diagnostic category of Substance Use Disorders (SUD). Rather than having two distinct disorders, the DSM-V will categorize the more general SUD according to level of severity, based on the number of diagnostic criteria that are met. Meeting 0 or 1 of the diagnostic criteria would result in no diagnosis, while meeting 2 to 3 would be categorized as a mild SUD, 4 to 5 as a moderate SUD, and 6 or more as a severe SUD. This classification scheme incorporating levels of severity within a single SUD diagnosis was accomplished by collapsing the DSM-IV Substance Abuse and Substance Dependence criteria. The DSM-IV criteria regarding recurrent legal problems was deleted from the SUD diagnosis, given concerns that this criterion had a lower prevalence rate than the other criteria, perhaps unfairly biased diagnoses of substance abuse in populations who have more involvement with the legal system, and would be difficult to consistently diagnose internationally, given differences in laws across international jurisdictions. An additional criterion of Substance Craving was added, given that research supports this as a key symptom of addictive disorders. The reasons for these changes are multiple, but combining the DSM-IV abuse and dependence criteria and grading according to the level of severity is thought to more accurately reflect the symptoms of individuals with substance use disorders, thereby having the potential to improve patient care and create greater precision in research. Also, there was a concern that the term "dependence" implied *physiological* dependence, which was not a criterion necessary to meet the DSM-IV diagnosis of Substance Dependence. Physiological dependence on some substances occurs as a normal response of neural systems that adapt to the exposure. Addiction, on the other hand, involves other adaptations that are distinct from those resulting in physiological dependence, wherein individuals experience loss of control and compulsively use substances despite their expectation of adverse consequences.

Finally, the DSM-V has moved away from the classification of neurocognitive disorders based on classic distinctions between dementia and amnestic syndromes, preferring a classification system that distinguishes between major and mild neurocognitive disorders. Thus, the DSM-IV disorders of Substance-Induced Persisting Dementia and Substance-Induced Persisting Amnestic Disorder will now fall under the classification of Substance-Induced Major Neurocognitive Disorder, with an

additional classification for Substance-Induced Mild Neurocognitive Disorder. There are other changes to the current Substance-Related Disorders section of the DSM-IV, and considered together, these changes will significantly alter the way that substance related disorders are characterized and diagnosed in the DSM-V.

CLINICAL CONSIDERATIONS

In order to accurately diagnose substance use disorders, a biopsychosocial history is required. Collateral information obtained from family members, case managers, social workers, physicians, and other professionals is helpful in this regard, since individuals who use substances often minimize the frequency, amount, and psychosocial impact of their use. This is particularly true when negative legal or employment consequences could result from a substance use diagnosis. Additionally, since there are acute and long-term effects of substance use on cognitive abilities, including learning and memory, clients may not be able to accurately report their history of use. In cases where the clinician suspects a substance-related disorder but also feels clients are minimizing their use, informant reports are particularly helpful. However, there are also several structured methods that might assist the clinician in obtaining a more accurate substance use and psychosocial history.

When available, a systematic review of medical records can provide valuable information, as they may provide insights into medical conditions that might be caused by and/or commonly co-occurring with substance use (e.g., liver disease, traumatic brain injury, and infectious diseases, such as hepatitis C), as well as provide information about prescription drugs that have a high potential for abuse, such as narcotics and benzodiazepines. Useful findings from laboratory tests may also be found in medical records, including results from tests that are specifically designed to detect the presence of substances in the system (e.g., urine toxicology), as well as test results that are consistent with the use of substances, such as elevated liver-function tests, which are associated with heavy alcohol use. There are also a number of psychometrically validated evaluation procedures that can assist in arriving at a diagnosis. For example, the Substance Abuse Subtle Screening Inventory-3 (SASSI-3; Miller & Lazowski, 1999) and the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) may help identify individuals who are at increased risk for substance abuse. Similarly, structured interviewing procedures like the Timeline Follow Back assessment procedure, can be used to assist the client in recalling instances of substance use. In this procedure, calendars are presented to the client covering the prior four months, and the client is asked to recall significant events that occurred over that time period; for example, birthdays, anniversaries, sporting events, etc. Clients are then instructed to recall instances of substance use that occurred proximal to these significant events, which provide memory anchors in a visually structured format to facilitate accurate recall of use. Detailed information on prior episodes of inpatient and outpatient treatment for substance abuse is also recommended and may facilitate dispositional planning.

While the diagnosis of substance-induced disorders relies heavily on many of the common elements previously discussed, in some cases more specialized procedures are also required. For example, in cases where the diagnosis of substance-induced persisting dementia is being considered, specialized medical procedures are commonly used in arriving at a diagnosis, including neurological evaluations, neuroimaging procedures, and neuropsychological evaluation, to document and profile cognitive strengths and weaknesses. In cases of mood, anxiety, developmental (e.g., attention-deficit/hyperactivity [ADHD]), and personality (e.g., antisocial) disorders that commonly occur in substance abuse and dependence, questionnaires (e.g., the Minnesota Multiphasic Personality Inventory-2 [MMPI-2], Wender-Utah Rating Scale) and semi-structured interviews (e.g., Structured Clinical Interview for DSM-IV SCID) designed to evaluate the presence and severity of these symptoms may also assist in arriving at a diagnosis. Specialized procedures may also be required for diagnosis of other disorders such as substance-induced sleep disorders (e.g., sleep studies) and sexual dysfunction (e.g., nocturnal penile tumescence-monitoring for male erectile dysfunction). Thus, for many substance-induced disorders, diagnosis is reached after extensive evaluation by a number of professionals, each with specialized expertise and functioning within the context of an interdisciplinary team.

Selection of an appropriate neuropsychological battery for individuals with substance-related disorders will depend on commonly referenced factors, such as time, resources, referral questions, setting (e.g., inpatient versus outpatient) and the specific characteristics of the individual client (e.g., physical and sensory limitations). In general, a test battery that emphasizes the domains that are known to be the most strongly affected in persons with substance-related disorders is recommended to enhance sensitivity, including episodic learning and memory, executive functions, information processing speed, motor coordination, and visuoperceptual skills. Among the various executive functions, particular emphasis might be placed on cognitive flexibility, impulsivity and disinhibition, novel problem-solving, and decision-making. Symptom validity tests and embedded measures of test-taking effort are also particularly valuable in the clinical evaluation of persons with substance-related disorders. Inclusion of performance-based and self- and other-report measures of neurobehavioral (e.g., Frontal Systems Behavior Scale [FrSBe]) and real-world (e.g., instrumental activities of daily living [ADLs]) may also facilitate diagnoses by documenting the real-world impact of observed neurocognitive problems (see Scott et al., this volume).

ORGANIZATION OF THE BOOK

The 18 chapters in this volume are organized into three sections that are designed to provide the reader with a translational overview of basic research and treatment findings regarding addictions, neuropsychological and neurological sequelae of the most common substances of abuse, and consideration of special issues that might confound the interpretation of neuropsychological test results.

Section I (Chapters 1–5) provides an overview of addictions, including diagnoses based on the DSM-IV, as well as the most current conceptualizations of addiction from the perspectives of psychobiology, genetics, behavioral and neuro-economics, and treatment. This section provides an understanding of translational research and uses findings from basic science to develop state-of-the-art evidence-based interventions and illustrates how these interventions might be modified given presenting neuropsychological deficits, which should assist clinicians with treatment planning. Additionally, this section is designed to provide the reader with a broad evidence-based conceptual framework for the chapters of the following sections II and III.

Section II (Chapters 6–12) reviews the most common substances of abuse, including coverage of structural and functional neuroimaging findings, epidemiological evidence, and neuropsychological sequelae. Substances included in this section represent the most commonly encountered drugs of abuse, including alcohol, cannabis, cocaine, methamphetamine, club drugs, opioids, and inhalants, with chapters written by some of the world's leading experts in these complex areas of clinical research. Some substances were not included in this section, such as nicotine, hallucinogens, and polysubstance use, because the literature either does not support long-term effects on cognition, or there is simply not enough evidence to allow for meaningful conclusions to be drawn about persisting neuropsychological effects as a consequence of their use.

Section III (Chapters 13–18) includes coverage of several special topics, including specific issues related to psychiatric (i.e., severe mental illness), medical (i.e., infectious disease), and neurological (i.e., traumatic brain injury) comorbidities, as well as special populations (i.e., adolescents) and the real-world impact of neuropsychological deficits in persons with substance-related disorders. Topics were selected for inclusion in this section if 1) they represented areas of common concern faced by clinical neuropsychologists, and 2) the potential neuropsychological effects of substance use and test results were confounded by the presence of these factors.

This overview of the history and diagnosis of substance-related disorders is intended to provide a brief background to the area of substance use and abuse and to illustrate the breadth of information that has come to bear on our understanding of the interplay between substance use and the brain over the past 30 years. This book endeavors to provide the most up-to-date information regarding substance use disorders, and assist clinicians in answering questions regarding impact of substance use on neuropsychological functioning.

References

Brecher, Edward M. and the editors of Consumer Reports (1972). Licit and Micit Drugs. The Consumers Union Report on Narcotics, Stimulants, Depressants, Inhalants, Halluncinogens, and Marijuana—including Caffeine, Nicotine, and Alcohol. Boston: Little, Brown and Company.

Brownstein, M. J. (1993). A brief history of opiates, opioid peptides, and opioid receptors. *Proceedings from the National Academy of Sciences*, *90*(12), 5391–5393.

Dasgupta, A. (2011). *The Science of Drinking: How Alcohol Affects Your Body and Mind*. Lanham, Maryland: Rowman & Littlefield.

Gallup Politics (2013). Record-High 50% of Americans Favor Legalizing Marijuana Use. Available at http://www.gallup.com/poll/150149/record-high-americans-favor-legalizing-marijuana.aspx.

Goldstein, G., & Chotlos, J. W. (1965). Dependency and brain damage in alcoholics. *Perceptual and Motor Skills*, *21*(1), 135–150.

Goldstein, G., & Chotlos, J. W. (1966). Stability of field dependence in chronic alcoholic patients. *Journal of Abnormal Psychology*, *71*(6), 420.

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2012). *Monitoring the Future: National Survey Results on Drug Use,1975–2011: Volume I, Secondary School Students*. Ann Arbor, MI: Institute for Social Research, the University of Michigan. Retrieved from http://monitoringthefuture.org/pubs/monographs/mtf-vol1_2011.pdf.

Jones, B., & Parsons, O. A. (1971). Impaired abstracting ability in chronic alcoholics. *Archives of General Psychiatry*, *24*(1), 71–75.

Levine D. G., Preston P. A., Lipscomb S. G. *Am J Psychiatry*. 1974 Sep;*131*(9):1036–7. A historical approach to understanding drug abuse among nurses.<http://www.ncbi.nlm.nih.gov/pubmed/4411648>

Lambert, W. G. (1996). *Babylonian Wisdom Literature*. Winona Lake, IN: Eisenbrauns.

Mack, A., & Joy, J. (2000). *Marijuana as Medicine? The Science Beyond the Controversy*. The National Academy Press. Washington, DC.

Marthe, M. L. (Ed.) (1997). Cannabis in Medical Practice: A Legal, Historical and Pharmacological Overview of the Therapeutic Use of Marijuana. Jefferson, NC: McFarland and Company.

McGovern P. E., Zhang J., Tang J., Zhang Z., Hall G. R., Moreau R. A., Nuñez A, Butrym E. D., Richards M. P., Wang C. S., Cheng G., Zhao Z., Wang C. *Proc Natl Acad Sci* U S A. 2004 Dec 21;*101*(51):17593–8.

Fermented beverages of pre- and proto-historic China.<http://www.ncbi.nlm.nih.gov/pubmed/15590771>

McGovern, P. E. (2009). *Uncorking the Past: The Quest for Wine, Beer, and Other Alcoholic Beverages*. Berkeley, CA: University of California Press.

McGovern, P. E., Hartung, H., Badler, V. R., Glusker, D. L., & Exner, L. J. (1997). The beginnings of winemaking and viniculture in the ancient Near East and Egypt. *Expedition*, *39*(1), 3–21.

Miller, T., & Hendrie, D. (2009). *Substance Abuse Prevention Dollars and Cents: A Cost-Benefit Analysis* (DHHS Pub. No. SMA 07-4298). Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Prevention.

Miller, F. G., & Lazowski, L. E. (1999). *The Adult SASSI-3 Manual*. Springville, IN: The SASSI Institute.

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. *Addiction*, *88*(6), 791–804.

Schiff, P. L. (2002). Opium and its alkaloids. *American Journal of Pharmaceutical Education*, *66*, 186–194.

Substance Abuse and Mental Health Services Administration (SAMHSA). (2010). *Results from the 2009 National Survey on Drug Use and Health: Vol. I. Summary of National Findings*. (Office of Applied Studies, NSDUH Series H-38A, DHHS Publication No. SMA 10-4856 Findings). Rockville, MD: SAMHSA.

Substance Abuse and Mental Health Services Administration. (2012). *Results from the 2011 National Survey on Drug Use and Health: Mental Health Findings* (No. HHS

Publication No. SMA 12-4725). Rockville, MD: Substance Abuse and Mental Health Services Administration.

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (Jan. 3, 2013). *The NSDUH Report: Trends in Adolescent Substance Use and Perception of Risk from Substance Use*. Rockville, MD: SAMHSA.

Tarter, R. E., & Parsons, O. A. (1971). Conceptual shifting in chronic alcoholics. *Journal of Abnormal Psychology*, *77*(1), 71–75.

World Health Organization (WHO). (2004). *Promoting Mental Health: Concepts, Emerging Evidence, Practice. Summary Report*. Geneva, Switzerland: WHO. Available at http://www.who.int/mental_health/evidence/en/promoting_mhh.pdf.

2

Neural Substrates of Substance Use Disorders

VERONICA BISAGNO AND JEAN LUD CADET

Drug addiction is a serious public health problem that manifests as a compulsive drive to take the drug without regard to severe adverse consequences (Volkow & Li, 2005). Drugs of abuse have well-known pharmacological consequences in the brain. Although these are necessary, they are not sufficient for the development and the maintenance of the addicted state. Other influencing factors include access to drugs, social environment, genetic predisposition, as well as other psychiatric comorbidities (Volkow, 2004). Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry, as defined by the American Society of Addiction Medicine (2013). Figure 2.1 provide a depiction of key brain regions and circuitry implicated in addiction. Dysfunctions within these brain circuits (Figure 2.1) are associated with characteristic biopsychosocial manifestations of addiction. Those include the inability to abstain from drug seeking and taking, unbearable craving, and behavioral impairments of various kinds, such as the inability to recognize the deterioration of interpersonal relationships (Volkow, Wang, Fowler, & Tomasi, 2012). The addicted state is also accompanied by repeated cycles of remission and relapses that are associated with adverse neuropsychiatric consequences, including depression and psychotic episodes, depending on the primary drug of choice (Wilson & Cadet, 2009). Without treatment or engagement in recovery activities, addiction is progressive and results in medical complications, risks of incarceration, social isolation, and/or premature death (Volkow et al., 2012).

Preclinical and clinical studies suggest that addiction is secondary to regional neuroadaptations in the brain. Preclinical models have consistently demonstrated the importance of the mesocorticolimbic brain reward system in drug dependence (Everitt & Robbins, 2006), while neuroimaging studies in drug-dependent

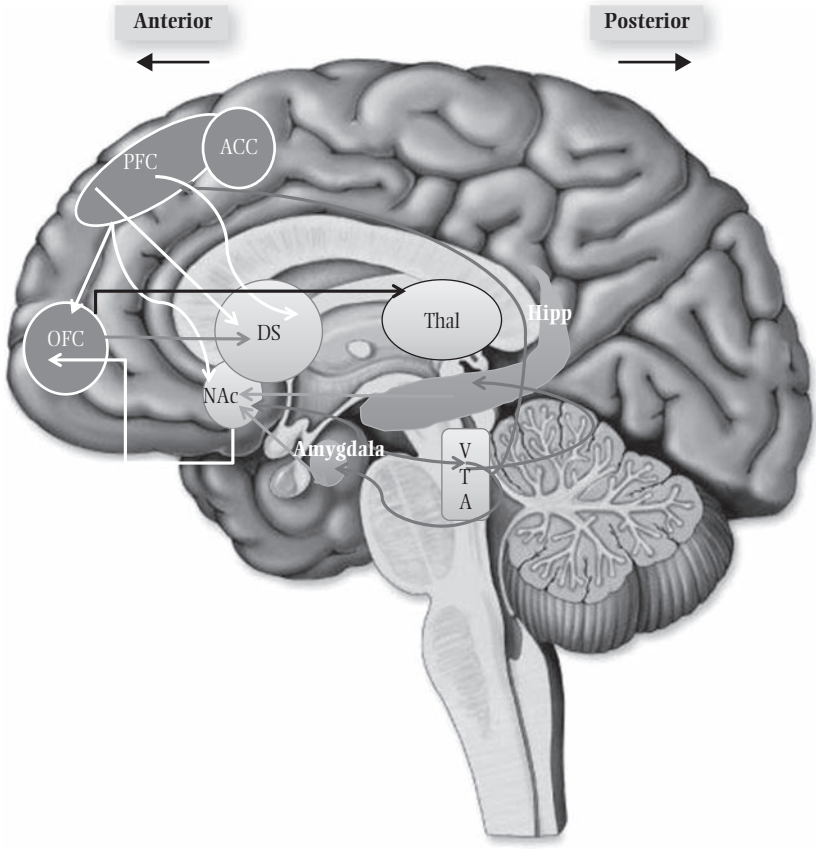

Figure 2.1 Mesocorticolimbic reward circuit. Regions of the brain that are involved in reward and addiction: the ventral tegmental area (VTA), ventral striatum (Nucleus Accumbens, Nac) involved in responding to rewarding stimulus; the amygdala (Amyg) and hippocampus (Hipp) that participate in memory functions; the mediodorsal thalamus (Thal), key component of thalamo-cortico-basal ganglia circuits working in tandem with the dorsal striatum (DS), implicated in aberrant habit learning disorders and the prefrontal cortex/orbitofrontal cortex (PFC/OFC) and anterior cingulate cortex (ACC) that participate in executive control and emotion regulation. (See color insert).

individuals have documented significant alterations in these same brain regions (Volkow & Li, 2005). The mesocorticolimbic components include:

1. the ventral tegmental area (VTA) and ventral striatum, which are involved in responding to rewarding stimuli (Wise, 2009);
2. the amygdala and hippocampus, which participate in memory functions, especially those related to learning cue and context associations (Malenka, 2003);
3. the mediodorsal thalamus, an intermediary node linking the midbrain and prefrontal cortex, and a key component of thalamo-cortico-basal ganglia circuits implicated in aberrant habit-learning disorders (Hyman, 2005); and

4. the prefrontal/orbitofrontal cortex (PFC/OFC) and anterior cingulate cortex, which regulate certain aspects of diverse emotions, cognition, and executive function, while exerting inhibitory control on various behavioral processes (Everitt & Robbins, 2006).

DOPAMINERGIC PROJECTIONS FROM THE VENTRAL TEGMENTAL AREA AND SUBSTANTIA NIGRA PARS COMPACTA

Drugs are taken because of their hedonic properties, and these rewarding effects are linked to their ability to increase dopamine (DA) in the dorsal striatum and nucleus accumbens (NAc) (Wise, 2009). DA neurons of the ventral midbrain can be divided into two main subpopulations: 1) the nigrostriatal projection, which arises from the substantia nigra pars compacta (SNpc) and projects to dorsal aspects of the striatum; and 2) the mesolimbic projection from the ventral tegmental area (VTA) to the NAc and other limbic regions (Figures 2.1 and 2.2). The DA neurons from the SNpc are involved mostly in motor functions, although

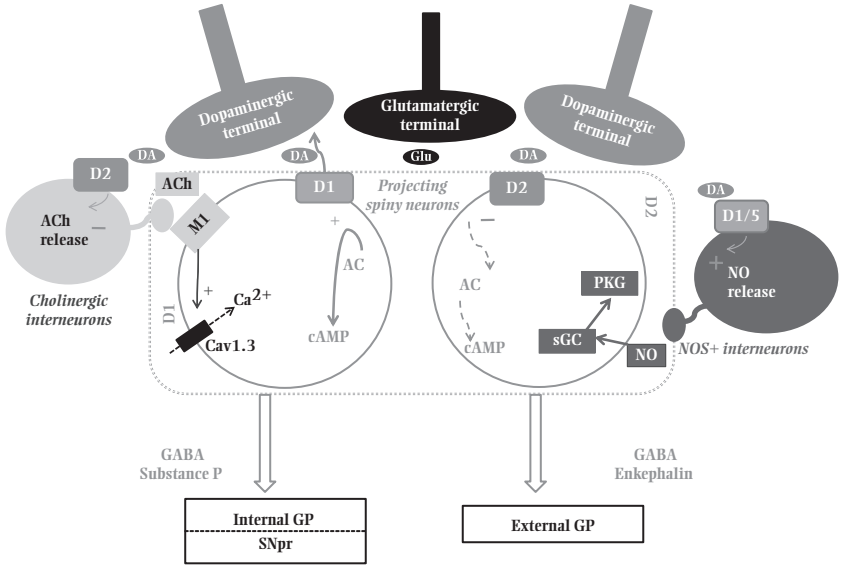

Figure 2.2 Cortical inputs reach GABA-releasing striatal output neurons where they exert glutamate-mediated excitation. Medium-size GABA-containing spiny neurons represent the main (95%) striatal neuronal population. They participate in the modulation of output signals from the basal ganglia via interaction with parvalbumin-containing GABA-releasing interneurons, NADPH diaphorase-, and somatostatin-positive interneurons. They also interact with large cholinergic aspiny interneurons. D1 receptors are found predominantly in striatonigral neurons of the "direct pathway," whereas D2 receptors are mainly expressed by the striatopallidal neurons of the "indirect pathway." *Abbreviations*: AC, adenylyl cyclase; Ach, acetylcholine; GP, globus pallidus; NO, nitric oxide, PKG, protein kinase G; sGC, soluble guanylyl cyclase.

recent evidence has accumulated to support an important role for these neurons in the rewarding process (Wise, 2009). Located medially to the SNpc, VTA DA neurons are known to play an important role in motivation and reinforcement. In contrast to SNpc DA neurons, they project to the ventral striatum, including the NAc core, shell, and olfactory tubercle, as well as to the amygdala, septum, hippocampus, and the PFC (Fields, Hjelmstad, Margolis, & Nicola, 2007; Ikemoto, 2007). In addition to DA neurons, the VTA contains a significant proportion of gamma-aminobutyric acid (GABA) producing neurons, which project to the PFC, NAc, and other brain regions (Fields et al., 2007). GABAergic VTA neurons also form local contacts onto both dopaminergic and nondopaminergic VTA neurons. Interestingly, a subset of VTA DA neurons expresses the vesicular glutamate transporter VGLUT2, indicating the potential to co-release of DA and glutamate (Hnasko, Hjelmstad, Fields, & Edwards, 2012).

DA neurons transmit DA signals via tonic and phasic modes (Grace, Floresco, Goto, & Lodge, 2007). In their tonic mode, DA neurons maintain steady, baseline levels of DA within downstream structures that are vital to their normal functions (Schultz, 2007). In their phasic mode, DA neurons increase or decrease their firing rates sharply for 100–500 milliseconds, causing large changes in DA concentrations in downstream structures, changes that can last for several seconds (Schultz, 2007).

INFORMATION ENCODED BY DA RELEASE

DA release is used to signal novel and motivationally relevant environmental events (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). For example, when an organism encounters a novel stimulus, whether it be a positive stimulus such as a food reward or a negative stimulus such as psychological stress, there are alterations in the activity of DA cells in the VTA and in DA release in axon terminal fields in the PFC, NAc, and/or amygdala (Hyman, 2005; Abercrombie, Keefe, DiFrischia, & Zigmond,1989; Lataster et al., 2011).

DA is also important for the motivation and reinforcement of actions. Drugs that interfere with DA transmission interfere with reinforcement learning, while manipulations that enhance DA transmission, such as brain stimulation and addictive drugs, often act as reinforcers (Wise, 2004; Wise, 2012). In addition, DA transmission is crucial for creating a state of motivation to seek rewards (Berridge & Robinson, 1998). DA release is not necessary for all forms of reward learning and may not always be "liked" in the sense of causing pleasure, but it is critical for causing goals to become "wanted" in the sense of motivating actions to achieve the desired goals (Berridge & Robinson, 1998; Palmiter, 2008). DA release might indeed be a *sine qua non* for the generation of motivated behaviors during diverse rewarding experiences. This idea is supported by observations that most DA neurons are strongly activated by unexpected primary rewards such as food and water, often producing phasic "bursts" of activity (Schultz, 2007) and phasic excitations including multiple spikes (Grace et al., 2007). Dopamine responses

might thus encompass a "reward prediction error" phenomenon that reports differences between the reward that is received and the predicted reward (Schultz et al., 2007). Thus, a larger than predicted reward might cause greater firing of DA neurons (positive prediction error), whereas a lesser reward might inhibit phasic firing (negative prediction error). A reward that is predictable has no influence on the firing of DA neurons (zero prediction error). These diverse set-ups or responses might influence the physiological responses to drugs of abuse that exert varied responses in animals, depending on environmental cues. This is consistent with the fact that DA reward responses are accompanied by synchronous phasic bursts, a response pattern that shapes DA release in target structures (Grace et al., 2007). These phasic bursts, in turn, influence learning and motivation in manner distinct from tonic DA activity (Grace et al., 2007; Schultz, 2007). Thus, it is not farfetched to suggest that humans treat rewarding and aversive events in similar physiological ways that reflect the predictability of motivational salience, whether positive or negative. Indeed, both rewarding and aversive events trigger attentional orienting, changes in cognitive processing, as well as increases in general motivation, because these are necessary to engage working memory to hold information in mind, to resolve conflict during decision-making, and to store the resulting behaviors in long-term memory (see Hyman, 2005; Bromberg-Martin et al., 2010).

DA neurons modulate signals related to processes such as goal seeking, engage motivationally salient situations, or react to alerting changes in the environment (Bromberg-Martin et al., 2010). DA neurons are proposed to transmit their signals to distinct brain structures in order to support distinct neural systems for motivated cognition and behaviors. Some DA neurons support brain systems that assign motivational value, promoting actions to seek rewarding events, avoid aversive events, and ensure that alerting events can be predicted and/or prepared for. Other DA neurons support brain systems that are engaged by motivational salience, including orienting to detect potentially important events, cognitive processing to choose a response and to remember its consequences, and motivation to persist in the pursuit of an optimal outcome. Ultimately, DA neurons tailor their signals to support multiple neural networks with distinct roles in motivational control. This discussion thus emphasizes the important role that DA systems might play in some of the common manifestations of various substances whose initial biochemical effects might be on presumably disparate neurotransmitter systems.

COMMON FEATURES OF DRUGS OF ABUSE ASSOCIATED WITH NAc DYSFUNCTIONS

The discovery that electrical stimulation of specific brain areas can induce reward (Olds, & Milner, 1954) has led to the theory that the mesotelencephalic DA system is the neurobiological substrate for the rewarding effects of both opiates and psychostimulants (Wise, 1978). Moreover, Di Chiara and Imperato (1988)

provided substantial evidence that addictive drugs consumed by humans increase DA concentrations in the rat mesolimbic DA system. These biochemical events might indeed be responsible for some of the similar clinical observations in humans who are addicted to drugs. Specifically, drugs of abuse can cause very similar biochemical, physiological, and molecular effects in various brain regions, including in the VTA and NAc (Nestler, 2005; Cadet, Jayanthi, McCoy, Beauvais, & Cai, 2010). Stimulants such as cocaine and methamphetamine directly increase dopaminergic transmission in the NAc by blocking the DA transporter or causing DA release through the vesicular monoamine transporter (Pontieri, Tanda, & Di Chiara, 1995; Xi et al., 2009). Opiates cause increased synaptic DA levels by inhibiting GABAergic VTA interneurons, a process that produces disinhibition of dopaminergic VTA neurons (Shabat-Simon, Levy, Amir, Rehavi, & Zangen, 2008). Other substances such as nicotine also appear to activate VTA DA neurons directly via stimulation of nicotinic cholinergic receptors on those neurons and indirectly via stimulation of its receptors on glutamatergic nerve terminals that innervate the DA cells (Dani & Zhou, 2001). Alcohol, by promoting GABAA receptor function, may inhibit GABAergic terminals in VTA and disinhibit VTA DA neurons (Boehm et al., 2004). Cannabinoid mechanisms appear to be more complex and involve activation of cannabanoid type 1 receptors on glutamatergic and GABAergic nerve terminals in the NAc and on NAc neurons themselves (Howlett et al., 2004).

These biochemical differences notwithstanding, there are many similarities in the brain regions that are influenced by these psychoactive drugs. There are, however, substantial differences in the neurobiological mechanisms and chronic neuroadaptations that are consequences of the self-administration of opiates and psychostimulants (Badiani, Belin, Epstein, Calu, & Shaham, 2011). In addition, different clinical patterns of drug abuse are also observed for cocaine and methamphetamine addiction (Simon et al., 2002), cannabis abuse (Hall & Degenhardt, 2009), and opiate addiction (Darke, 2012). These clinical, biochemical, and molecular differences need to be taken into consideration when approaching the discussion of the neural substrates of drug addiction and while planning therapeutic approaches to individuals addicted to these various substances. These differences might also impact on the neuropsychological sequelae of these licit and illicit drugs.

The NAc is part of the ventral striatal complex and serves as a critical region where motivations derived from limbic regions interface with motor control circuitry to regulate appropriate goal-directed behavior (Wise, 2004; Hyman, 2005). Like other parts of the ventral striatal complex, the NAc receives extensive excitatory afferents from the cerebral cortex and thalamus. It projects to the ventral pallidum, which innervates the mediodorsal and other thalamic divisions, thus completing cortico–striato–pallidal–thalamocortical loops (Zahm & Brog, 1992; O'Donnell, Lavín, Enquist, Grace, & Card, 1997). Excitatory cortical afferents to the NAc typically synapse onto the spines of medium spiny neurons. The so-called triad of elements—spine, glutamate synapse, and DA synapse—creates the potential for DA to modulate discretely specific sources of glutamate transmission onto distal dendritic compartments as opposed to a

more generalized effect on overall cell excitability (Sesack, Carr, Omelchenko, & Pinto, 2003).

It is also noteworthy that there is indication that these dopaminergic and/or glutamatergic pathways that interact at the levels of the VTA, NAc, and other limbic regions might also be the generators of the positive emotional effects of natural rewards, such as food, sex, and social interactions (Volkow et al., 2012; Wise, 2012). These same regions appear to be the culprits that foster compulsive food consumption (Wang, Volkow, Thanos, & Fowler, 2009), pathological gambling (van den Brink, 2012), and sexual addictions (Blum et al., 2012), among other compulsive behaviors such as Facebook addiction (Andreassen, Torsheim, Brunborg, & Pallesen, 2012).

ROLE OF THE NIGROSTRIATAL AND CORTICOSTRIATAL PATHWAYS IN DRUG ADDICTION

In addition to the mesoaccumbens systems, the nigrostriatal dopaminergic pathway appears to be involved in addictive processes. The dorsal striatum represents the main input into the basal ganglia (Graybiel, Aosaki, Flaherty, & Kimura, 1994; Figure 2.2). In addition to inputs from the SNpc, striatal projection neurons receive a large convergence of afferents from all areas of the cortex, which has a crucial integrative and computational role that mediates, in part, sequences that direct acquisition of motor skills (Calabresi, Picconi, Tozzi,, & Di Filippo 2007), the selection and initiation of actions (Graybiel et al., 1994), and stimulus–response (habit) learning, including drug-taking behaviors (White & McDonald, 2002; Everitt & Robbins, 2006). Dopaminergic afferents from SNpc also converge on these cells, and there is evidence that glutamate and DA receptors can form heterodimers that are highly organized molecular complexes where different classes of receptors are clustered (Fuxe et al., 2008). These observations support the idea that the dorsal striatum might participate in important integrative steps in the development and maintenance of drug addiction.

These integrative processes probably occur at the level of medium-size GABA-containing spiny neurons that represent the main (95%) neuronal population of the striatum (Figure 2.2), where they modulate the output signals of the basal ganglia through interaction with three major subclasses of interneurons: fast-spiking, parvalbumin-containing, GABA-releasing interneurons; low-threshold spike, nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) diaphorase- and somatostatin-positive interneurons; and large cholinergic aspiny interneurons (Kawaguchi, Wilson, Augood, & Emson, 1995; Tepper & Bolam, 2004). Cortical inputs reach GABA-releasing neurons that output from the striatum, on which they exert a powerful glutamate-mediated excitatory influence (Calabresi et al., 2007). Long-lasting, activity-dependent synaptic changes are thought to underlie the ability of the brain to translate experiences into memories and seem to represent the cellular model underlying learning and memory processes.